

Remarks

Claims 17-35 are pending in the subject application. Applicant acknowledges that claims 21, 23 and 27-29 have been withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicant has canceled claims 18, 19 and 27-29, amended claims 17, 20-26 and 33 and added new claims 36-41. Support for the amendments and new claims can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 17, 20-26 and 30-41 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Claim 33 is objected to because of informalities. In accordance with the Examiner's suggestion, Applicant has hyphenated the phrase "cell derived". Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

The Office Action objected to the specification because of informalities in the use of trademarks and it contained embedded hyperlinks or other forms of browser executable code. Applicant respectfully submits that the issue regarding the embedded hyperlink is moot in view of the amendment made to the specification. The Office Action indicates that the term "Hybond" appears on page 12, line 13 of the subject application. Applicant respectfully asserts that the term "Hybond" does not appear on page 12 nor elsewhere in the subject application. Accordingly, reconsideration and withdrawal of the objections is respectfully requested.

Claims 17-20, 22, 24-26 and 30-35 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicant respectfully asserts that the claims as filed are definite and have addressed each aspect of the rejection separately.

Claims 17-20, 22, 24-26 and 30-035 are rejected for omitting essential steps, such omission amounting to a gap between the steps. By way of this Amendment, claim 17 has been amended to further recite that the method be performed under conditions suitable for expression of the polypeptide. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Claim 17 is rejected because the term “production cycle” could not be found in the specification. Applicant has amended the claim and introduced the term “production phase”. The definition for this phrase can be found on page 6, lines 15 to 18 of the subject application where it is stated: “The term ‘production phase’ means a period during which cells are producing high amounts of recombinant polypeptide. A production phase is characterized by a lower cell division than during a growth phase and by the use of medium and culture conditions designed to maximize polypeptide production.” It is respectfully submitted that this phrase is not indefinite and reconsideration of the rejection of record is respectfully requested.

Claim 20 is rejected because it is unclear how the term “active fraction” relates to a protein. Applicant has deleted this term from the claim, thereby the rejection is moot.

Claims 20, 22 and 24-26 are confusing in the recitation of “circularly permuted derivative.” Applicant has deleted this term from the claim, thereby the rejection is moot. Accordingly, reconsideration and withdrawal of each of the rejections set forth under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 17-20, 22, 24-26, 30 and 32-34 are rejected under 35 U.S.C. § 102(b) as anticipated by Browning *et al.* (WO 00/036092). The Office Action notes that Browning *et al.* teach improving the production of recombinant proteins in CHO cells by lowering the cell culture temperature to between about 27 to about 35, preferably 27 to 32 degrees C, and purifying the protein. The examiner also states that although Browning *et al.* do not specifically teach TBP-1, the instant claims recite fragments, or active fragments thereof. Applicant respectfully asserts that the Browning *et al.* reference does not anticipate the claimed invention. For example, Browning *et al.* fail to teach culturing mammalian cells in serum free medium and culturing cells at temperatures of about 25°C or 26°C. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) is respectfully requested.

Claims 18-20, 31 and 35 are rejected under 35 U.S.C. § 103(a) as obvious over Browning *et al.* (WO 00/036092) in view of Nophar (1990). The Office Action asserts that the Nophar reference teaches the TBP-1 of SEQ ID NO:1. The Office Action states that given the teachings of decreased temperature on the protein of Browning *et al.*, it would have been obvious for one of ordinary skill in the art to have lowered the temperature in CHO cells regardless of the recombinant protein desired to

be produced and that “obvious to try” may be an appropriate test in situations. Particularly, the Office Action argues that “when there is motivation to solve a problem and there are a finite number of identified predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense”. Applicant respectfully asserts that the claimed invention is not obvious over the cited references and that the Office Action has failed to identify a problem that was recognized in the art and could be solved by the combination of references. Furthermore, even if an art recognized problem was demonstrated to exist with respect to the production of TBP-1, the amount of polypeptide produced according to the claimed invention is unexpectedly different as compared to that disclosed in the combination of prior art references.

As set forth in the Patent Office’s “Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*” (72 Fed. Reg. 57526, 57532 (2007)):

To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:

- (1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
- (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
- (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and
- (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

In this case, it is respectfully submitted that the Office Action fails to establish that the art recognized that there was a problem or need in the art for producing TBP-1 in higher yields of active protein and that there were more than a “finite number of identified, predictable potential solutions”. As noted in

the Office Action, Browning *et al.* teaches that reducing the temperature at which receptor-Ig fusion proteins were produced (via cultivation of mammalian cells at temperatures of about 27°-32°C) resulted in significantly less misfolded (inactive) smaller forms of the fusion proteins. Indeed, Browning *et al.* indicate: “The present invention relates to methods for the expression of high yields of the form of protein-Ig fusions having high affinity binding to its ligand, referred to herein as the ‘active’ form, the form, by culturing hosts transformed with DNA encoding the desired fusions in a culture system at a low temperature thereby minimizing the amount of misfolded or misbridged protein forms”(see page 4, lines 4-8). Further, Browning *et al.* make numerous references to “dead protein” or “inactive protein” throughout the Examples discussed in the PCT application (see, for example, Examples 3, 6, 7 and Table II) and Table II indicates that about 50% of the protein produced at 37°C is inactive. However, there is no showing or evidence in the instant Office Action that protein misfolding or the production of inactive forms of the claimed TBP-1 polypeptide was an art recognized problem at the time this application was filed. Additionally, the as-filed specification indicates that a variety of parameters can affect protein production at low temperatures. These include promoters used to drive expression of a protein and the cell lines that are to be cultivated (see page 1, lines 19-20). Accordingly it is respectfully submitted that a *prima facie* case of obviousness has not been established in this instance and reconsideration and withdrawal of the rejection of record is respectfully requested.

Even assuming, *arguendo*, that a *prima facie* case of obviousness has been established by the cited combination of references, Applicant respectfully submits that the increased amounts of TBP-1 produced in accordance with the claimed invention is unexpectedly different than would be expected upon the application of the cited references. As indicated in Browning *et al.*, lowering the cultivation temperature from 37°C to about 27°C resulted in about a 3.3 fold increase in the production of active protein (see page 18, lines 26-29). In contrast, Example 1 of the instant application (page 12) demonstrates that increased production of TBP1 was obtained at 25°C as compared to 37°C (a temperature at which very little protein was secreted (see also Figure 2)). As indicated in Figure 3, about an 8-fold increase of specific productivity was observed at 25°C without an alteration in the quality of the protein in terms of glycosylation (see Figures 7 and 8) and productivity increase of up to 10-fold were also observed (see page 16, lines 19-22). As shown in

Table 1 (Example 2, page 16), the S-index (which is an indicator of the degree of sialylation of the protein) was comparable at 25° C and 37° C. Accordingly, it is respectfully submitted that the claimed invention is not *prima facie* obvious over the cited combination of references and reconsideration and withdrawal of the rejection is respectfully requested.

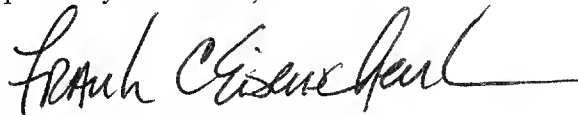
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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